

Synthesis, Characterization and Biological Evaluation of Some 1,3,5-Trisubstituted-2-pyrazolines

K. ISHWAR BHAT* and DOBARIYA UMESH KUMAR P.

Department of Pharmaceutical Chemistry, N.G.S.M. Institute of Pharmaceutical Sciences, Paneer, Deralakatte, Mangalore-574 160, India
E-mail: bhatishwar@yahoo.co.in

A new series of 1,3,5- trisubstituted pyrazolines (**7a-j**) were synthesized by the condensation of various substituted chalcones (**6**) with substituted aniline acetyl hydrazides (**3**) derived from various disubstituted anilines (**1**) and characterized by IR, ¹H NMR and Mass spectroscopic analysis. The compounds were evaluated for antimicrobial activities.

Key Words: Heterocyclic compound, Hydrazides, Chalcones, Pyrazolines, Antibacterial, Antifungal activity.

INTRODUCTION

Many important biochemical compounds and drugs of natural origin contain heterocyclic ring structures. A large number of heterocyclic compounds are essential to life. The presence of heterocyclic ring in such diverse type of compounds is strongly indicative of profound effects of such molecules to exert physiological activity and reorganization of this is reflected abundantly in efforts to find useful synthetic drugs. Though the heterocyclic compounds were recognized laterally their biological activities attracted the researchers. Intensive research in diverse heterocyclic derivatives continues to yield new medicinal agents.

Among a wide variety of heterocycles that have been explored for developing pharmaceutically important molecules such as chalcones, pyrazolines, aminopyrimidines and pyrimidinethiones have played an important role in medicinal chemistry.

The chemistry of cyclized heterocyclic systems especially containing pyrazoline moiety have been largely investigated because they are effective in many pharmacological areas. Their derivatives possess a great number of biological activities such as antibacterial, antiviral, antitumor, antitubercular¹, central nervous system and immunosuppressive², analgesic³, antiulcer⁴ and antiinflammatory⁵.

EXPERIMENTAL

Melting points were taken in open capillaries in liquid paraffin bath and are uncorrected. IR spectra was recorded in Shimadzu Perkin-Elmer 8201 PC IR Spectrometer using a thin film on potassium bromide pellets. The ¹H NMR spectra were recorded on Bruker Avance II 400 NMR Spectrometer using CDCl₃. Chemical shift values are reported as values in ppm relative to TMS ($\delta = 0$) as internal standard.

The FAB mass spectra were recorded on Jeol SX-102/DA-6000 Mass spectrometer using argon/xenon (6Kv, 10Ma) as the FAB gas.

In the present work, substituted pyrazolines (**7**) have been synthesized by the condensation of aryloxy acetyl hydrazide (**3**) with various chalcones (**6**) in presence of glacial acetic acid. The synthesis consists of 3 steps, which are as follows:

Step-I: Preparation of ethyl aryloxy acetate (2): A mixture of eugenol (0.1 mol), chloro ethyl acetate (12.25 g, 0.1 mol) and anhydrous potassium carbonate (19.5 g, 0.15 mol) in dry acetone were refluxed on a water bath for 16 h at 50 °C. The resultant reaction mixture was cooled and filtered. From the filtrate, excess of acetone was removed by distillation. The reaction mixture of filtrate was then poured on to the ice-cold water and stirred well. Organic layer was extracted with ether and further the ether layer was washed with water and dried over anhydrous sodium sulphate followed by the removal of etheral layer by drying on a water bath. The resultant liquid is collected to get the pure ethyl aryloxy acetate.

Preparation of aryloxy acetyl hydrazide (3): A mixture of ethyl aryloxy acetate (0.05 mol) and hydrazine hydrate (99 %, 3.525 g, 0.075 mol) in ethanol (100 mL) were refluxed on a water bath for 16 h. From the resultant mixture excess of ethanol was removed by distillation. On cooling, the resultant mixture of aryloxy acetyl hydrazide separates in the form of white needle like crystals and recrystallized from ethyl alcohol⁴.

Step-II: Synthesis of chalcones (6) [substituted 1,3-diphenyl propen-1-one] from substituted aldehydes (4) and substituted acetophenones (5): Substituted aromatic aldehydes (0.01 mol) was made to react with substituted acetophenones (0.01 mol) in presence of ethyl alcohol (25 mL) and 40 % sodium hydroxide (3 mL). The mixture was stirred for 24 h. The reaction mixture was poured into ice water and acidified with dilute hydrochloric acid. The solid product was filtered and crystallized from ethanol⁶.

Step-III: Synthesis of substituted pyrazoline derivatives (7): Chalcone (0.01 mol) and aryloxy acetyl hydrazide (0.02 mol) in 20 mL of glacial acetic acid was refluxed for a period of 10 h and cooled. Excess of solvent was removed under reduced pressure and the reaction mixture was poured into 250 mL of ice-cold water. The product obtained was filtered, washed with cold water and recrystallized from ethanol^{7,8} (**Scheme-I**). The physical characteristics of the synthesized substituted pyrazoline derivative are given in Table-1. The spectral data of some of the synthesized compounds (**7a-d**) are given below:

7a: IR(KBr, ν_{\max} , cm^{-1}): -NH (*str.*) 3182, -CH (*str.*) 2923, -C=O (*str.*) 1668, C=N (*str.* in pyrazoline) 1338, N-N (*str.*) 3107. ¹H NMR (δ ppm) 6.89-8.00 (11H, m, Ar), 2.17 (3H, s, CH₃), 7.94 (1H, s, NH), 2.88-2.92 (2H, m, CH₂ of pyrazoline), 9.82 (1H, s, OH). Mass m/z molecular peak-454, base peak-226.

7b: IR (KBr, ν_{\max} , cm^{-1}): -NH (*str.*) 3251, -CH (*str.*) 2922, -C=O (*str.*) 1660, C=N (*str.* in pyrazoline) 1329, N-N (*str.*) 3050. ¹H NMR (δ ppm) 7.01-8.02 (11H, m, Ar), 1.25-1.28 (2H, m, CH₂), 2.41 (2H, m, CH₂ of pyrazoline), 3.85 (1H, m, CH of pyrazoline). Mass m/z M⁺+1 peak-432, base peak-95.

TABLE-1
PHYSICAL DATA OF SUBSTITUTED PYRAZOLINE DERIVATIVES

Compd.	Colour	m.p. (°C) / Yield (%)	R ₁	R ₂	R ₃	m.f. / (m.w.)
7a	Brown	89-92 (54.34)	-Cl (<i>m,p</i>)	-CH ₃ (<i>p</i>)	-OH (<i>p</i>)	C ₂₄ H ₂₁ N ₃ O ₂ Cl ₂ (454.35)
7b	Brown	95-97 (60.53)	-CH ₃ (<i>o,p</i>)	-CH ₃ (<i>p</i>)	-Cl (<i>p</i>)	C ₂₆ H ₂₆ N ₃ O ₂ Cl (431.96)
7c	Reddish brown	103-106 (58.63)	-CH ₃ (<i>o,p</i>)	-OCH ₃ (<i>p</i>)	-NO ₂ (<i>m</i>)	C ₂₆ H ₂₆ N ₄ O ₄ (458.51)
7d	Yellow	98-102 (65.12)	-Cl (<i>m,p</i>)	-OH (<i>o</i>)	-Cl (<i>p</i>)	C ₂₃ H ₁₈ N ₃ O ₂ Cl ₃ (474.77)
7e	Black	90-93 (54.28)	-CH ₃ (<i>o,p</i>)	-CH ₃ (<i>p</i>)	-OH (<i>p</i>)	C ₂₆ H ₂₇ N ₃ O ₂ (413.51)
7f	Pale yellow	105-107 (70.84)	-Cl (<i>m,p</i>)	-OCH ₃ (<i>p</i>)	-NO ₂ (<i>m</i>)	C ₂₄ H ₂₀ N ₄ O ₄ Cl ₂ (499.35)
7g	Black	87-89 (59.54)	-CH ₃ (<i>o,p</i>)	-OH (<i>o</i>)	-Cl (<i>p</i>)	C ₂₅ H ₂₄ N ₃ O ₂ Cl (433.93)
7h	Pale yellow	85-87 (60.00)	-Cl (<i>m,p</i>)	-CH ₃ (<i>p</i>)	-Cl (<i>p</i>)	C ₂₄ H ₂₀ N ₄ O ₃ Cl ₂ (483.35)
7i	Yellow	108-110 (68.73)	-CH ₃ (<i>o,p</i>)	-OH (<i>o</i>)	-NO ₂ (<i>m</i>)	C ₂₅ H ₂₄ N ₄ O ₄ (444.48)
7j	Ash coloured	106-109 (70.34)	-Cl (<i>m,p</i>)	-OH (<i>o</i>)	-NO ₂ (<i>m</i>)	C ₂₃ H ₁₈ N ₄ O ₄ Cl ₂ (485.3)

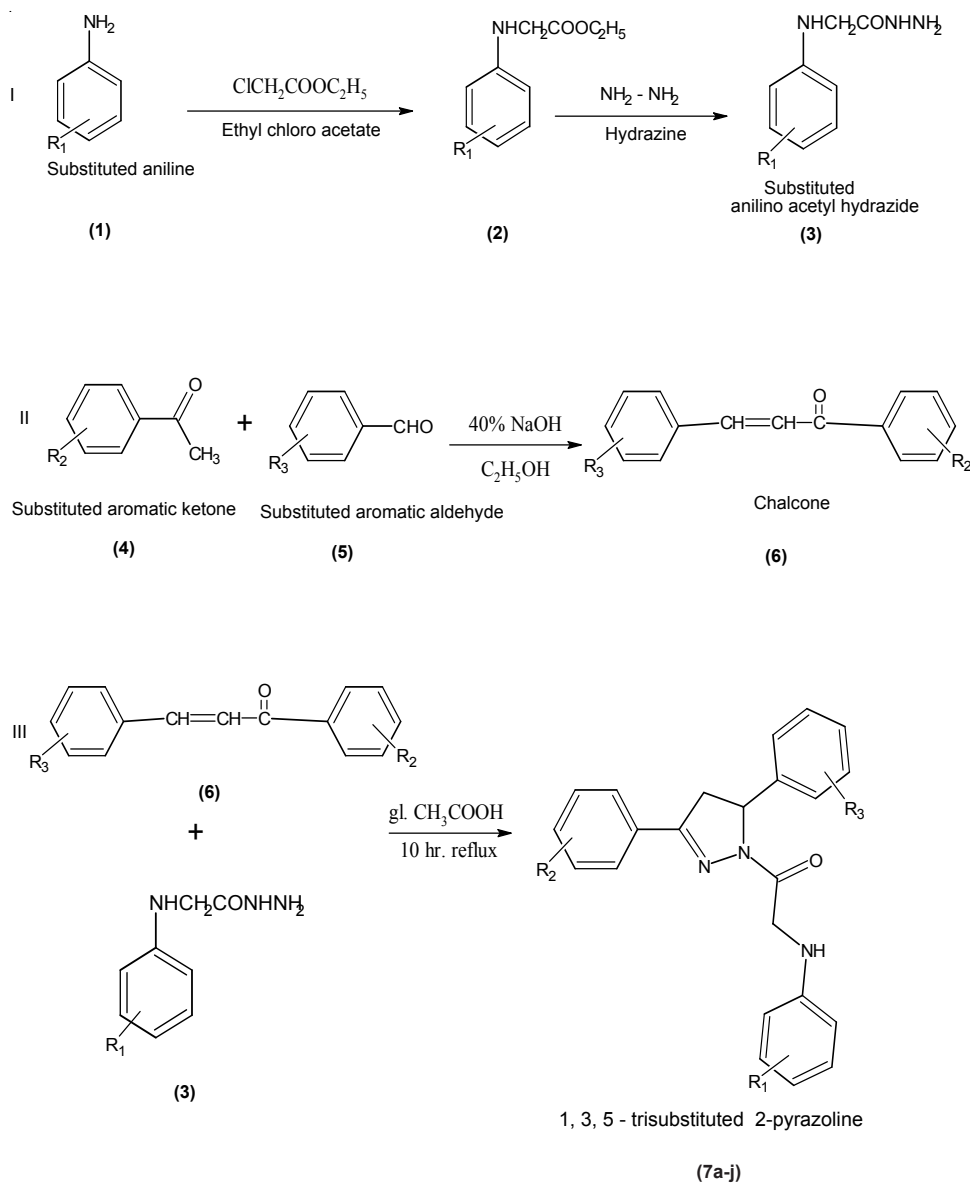
7c: IR (KBr, ν_{\max} , cm^{-1}): -NH (*str.*) 3225, -CH (*str.*) 2851, -C=O (*str.*) 1666, C=N (*str.* in pyrazoline) 1348, N-N (*str.*) 3040. ¹H NMR (δ ppm) 6.93-8.01 (11H, m, Ar), 8.51 (1H, s, NH), 2.31-2.34 (2H, m, CH₂ of pyrazoline), 3.83-3.87 (1H, m, CH of pyrazoline), 2.17 (3H, s, 2CH₃), 1.84 (2H, s, CH₂), 3.91 (3H, s, OCH₃). Mass m/z M⁺+2 peak-460, base peak-95.

7d: IR (KBr, ν_{\max} , cm^{-1}): -NH (*str.*) 3299, -CH (*str.*) 2921, -C=O (*str.*) 1668, C=N (*str.* in pyrazoline) 1366, N-N (*str.*) 3106. ¹H NMR (δ ppm) 6.95-7.93 (11H, m, Ar), 2.85-2.90 (2H, m, CH₂ of pyrazoline), 5.45-5.49 (1H, m, CH of pyrazoline), 12.78 (1H, s, OH), 7.84 (1H, s, NH). Mass m/z molecular peak-474, base peak-95.

Antimicrobial activity studies: The compounds **7a-j** were screened for their antibacterial activity against *B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa* and anti-fungal against *Candida albicans* by cup plate method using DMF as a solvent at concentration of 50 μg . The activity was compared with known standard drugs gentamycin and griseofulvin, respectively at same concentration⁹ (50 μg).

RESULTS AND DISCUSSION

All the synthesized pyrazoline derivatives have shown moderate to good antibacterial and antifungal activity in comparison to that of the standard drugs gentamycin and griseofulvin (Table-2).



Scheme-I

Compounds **7b**, **7c**, **7d** and **7h** have shown significant antibacterial activity and the compounds **7f**, **7g**, **7i** and **7j** have shown moderate activity when compared with that of the standard drug gentamycin.

Compounds **7b**, **7c**, **7e** and **7f** have shown moderate antifungal activity when compared with that of the standard drug griseofulvin.

TABLE-2
DATA OF ANTIMICROBIAL ACTIVITY OF SUBSTITUTED
PYRAZOLINE DERIVATIVES

Compd. No.	Diameter of zone of inhibition (mm)				
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
7a	17	16	18	16	9
7b	15	17	14	15	15
7c	14	16	14	13	14
7d	16	14	17	15	11
7e	7	10	8	–	13
7f	14	15	13	10	14
7g	14	13	11	10	12
7h	16	17	14	12	11
7i	15	14	15	12	7
7j	17	14	14	15	13
Gentamycin	21	20	21	22	–
Griseofulvin	–	–	–	–	20

(–) Indicates no inhibition zone (no activity).

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